UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,715	11/07/2001	Brent W. Weston	5470-259CT	8629

20792 7590 03/25/2004

MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER	
SCHULTZ, JAMES	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,715	WESTON ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-11,16-18 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-11,16-18 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-7-2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of application

The restriction requirement mailed October 3, 2003 has been withdrawn. The restriction was set forth based on the large number of sequences being claimed for use in the instant methods. However, applicants pointed out that these compounds were examined in the parent application; accordingly, this search was utilized and the restriction thus withdrawn.

Claim Rejections - 35 USC § 112

Claims 9-11, 16-18 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of Fucosyltransferase 3 and 6 (FUT3 AND FUT6 respectively) expression *in vitro*, does not reasonably provide enablement for cancer treatment via antisense-mediated inhibition of FUT3 and FUT6 expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The above invention is drawn to methods of treating cancer comprising administering an oligonucleotide of any of SEQ ID NOS: 1-24, targeted to FUT3 or FUT6, in a patient in need thereof, wherein the cancer is selected from a variety of cancer types. The specification teaches a method of using a large transfected antisense fragment to inhibit the expression of FUT3 AND

FUT6 in cells *in vitro*, and also teaches that injection of these cells transformed to express and antisense transcripts targeted to FUT3 and FUT6 into the spleen do not metastasize to the liver.

The specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to use the antisense oligonucleotides in *in vivo* environments. This is maintained because a person skilled in the art would recognize that predicting the efficacy of cancer treatment using an antisense oligo *in vivo* based on the use of a different antisense nucleotide sequence on cells injected into an organism is unpredictable. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* in methods of treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of antisense treatment.

A recent (2002) review article by Braasch et al. concludes that major obstacles persist in the art of using antisense oligos in treating disease: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. specifically identify 3 factors that contribute

to the unpredictable efficacy of using antisense compounds in general: 1) the variable capability of antisense oligonucleotides to access sites within the mRNA to be targeted; 2) problems pertaining to the delivery and uptake of the antisense oligos by cells, with the result that "the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death"; and 3), that "oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism."

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. elaborates, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target, and that "[a]ttempts to describe the *in vivo* structure of RNA, in contrast to DNA, have been fraught with difficulty." (Page 3161, second column).

These comments are considered particularly relevant to the instant situation, where applicants have not exemplified the use of any of SEQ ID NOS: 1-24, either *in vitro* or *in vivo*. While applicants have provided generalized guidance in regards to the use of SEQ ID NOS: 1-24 (which are between 20 and 25 nucleotides long) in the treatment of cancer, this is not considered

enabling, because, per the above, it is impossible to tell *a priori* whether any of these oligos have access to their target sites on the FUT3 or FUT6 transcripts. In the instant application, applicants have exemplified quite a different construct. Applicants have actually exemplified FUT3 and FUT6 inhibition via vector mediated-expression of large antisense fragments, none of which are close in length to SEQ ID NOS: 1-24 as claimed. Thus, because the inhibitory activity of an oligo depends unpredictably on the structure of the nucleic acid, the use of SEQ ID NOS: 1-24 in treating cancer is considered to be unpredictable, particularly since applicants have not exemplified their use in such methods.

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states that "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379). Gewirtz adds that [t]he other major problem in this field is the ability to deliver ODN (oligodeoxynucleotides) into cells and have them reach their target . Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient."

Applicants specification does not provide any teachings that would allow one of skill in the art to predict whether the instant SEQ ID NOS: 1-24 will find the appropriate cells and penetrate the cell membrane. While applicants have shown that a cell-line transfected *in vitro* can express an antisense transcript that inhibits FUT3 or FUT6, and have also shown that these cells do not metastasize when injected *in vivo*, this is not considered to be analogous to delivery of antisense oligos 20-25 nucleotides long in the treatment of cancer. This is because the transformed cell line is transfected first *in vitro*, which differs from the treatment of cancer which must necessarily happen *in vivo*. Because the cell-lines' introduced antisense fragment inhibits its intracellular target only after transfection *in vitro*, and because delivery of antisense oligos *in vivo* is considered to be a major source of unpredictability in the use of antisense oligos in any treatment, the instant teaching does not speak to whether any oligo of SEQ ID NO: 1-24, which differ dramatically in structure from the large vector-based antisense fragment, would traverse the cell membrane upon injection and inhibit its target.

Further complications that are unresolved in the field of antisense therapeutics are set forth by Branch et al., who discusses the problems pertaining to non-specific oligo interactions that lead to artifactual phenotypes during *in vivo* antisense administration: "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Applicants exemplification of a cell-line transfected *in vitro* to express a large antisense fragment that acts only intracellularly thus does not provide any resolution to the issue of non-antisense effects and artifactual phenotypes as discussed above. This is because the exemplified large antisense fragment is contained intracellularly, and is thus not susceptible to binding to plasma proteins or activating an immune response, in contrast to the instantly claimed methods of administering an oligo of SEQ ID NO: 1-24, which would be susceptible to such binding and immune activation.

Further, regarding the therapeutic benefit of antisense technology in general, Branch states that "in fact, nucleic acid drugs should not be thought of as magic bullets. Their therapeutic use will require vigilant monitoring. Compared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs extend only across a narrow concentration range. Both *in vitro* and *in vivo*, less than a factor of ten often separates the concentration producing no antisense effect form that producing the full antisense effect. Steep dose-response curves commonly indicate that a drug has multiple, synergistic mechanisms of action. A drug with a narrow therapeutic window can be potent and extremely valuable, but can also be tricky to use safely. Since the ratio of antisense to non-antisense effects drops sharply outside a restricted concentration range, it will be challenging to obtain consistent therapeutic benefit (Page 46, second column).

Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

Finally, Branch states that "[i]t is not yet clear whether *in vitro* screening techniques of the sort used by Milner and co-workers will identify ODNs that are effective *in vivo*. With so many possible sequences to choose from, and the likelihood that *in vitro* studies will not always predict *in vivo* efficacy, straightforward new screening techniques need to be developed for use in cells."

Thus, it is maintained that the use of *in vitro* antisense transfection techniques and xenografts using these does not enable claims directed to the *in vivo* administration of antisense oligos for therapeutic use *in vivo*. One of skill would not find the guidance provided in the specification in the form of *in vitro* examples, xenografts using same, and broad prophetic treatment regimens enough to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, as exemplified in the references above.

Since the specification fails to provide any real guidance for the methods of using antisense *in vivo* or in the successful treatment or prevention of such a broad range of cancers, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of those sequences that are successfully delivered to target sites in appropriate cells and /or tissues such that inhibition is achieved and treatment attained. In the absence of any

real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James Douglas Schultz, PhD

SEAN McGARRY
PRIMARY EXAMINER
1635